IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., Plaintiff/Counter-Defendant, v. ILLUMINA, INC., Defendant/Counter-Plaintiff.	C.A. No. 04-901-JJF **REDACTED VERSION**

AFFYMETRIX, INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

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INTRODUCTION

Illumina's proposed constructions violate well-established principles of claim construction. These errors include (1) ignoring definitions of claim terms in the specification,[1] (2) importing limitations from the specification,[2] (3) construing terms to exclude described embodiments,[3] (4) relying on snippets of the prosecution history to limit claims where there is not a clear disavowal,[4] and (5) using extrinsic evidence that is taken out of context and inconsistent with the intrinsic evidence.[5]

Illumina's strategy is to obtain claim constructions that limit the claims of the patents-in-suit to Affymetrix's commercial embodiments. Neither the law nor the intrinsic evidence supports this attempt. As Affymetrix demonstrates, application of the rules of claim construction set out in *Phillips* and other Federal Circuit decisions confirms that Affymetrix's proposed constructions are proper and should be adopted.

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1 *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*) ("Consistent with that general principle, our cases recognize that the specification may reveal a special definition given to a claim term by the patentee that differs from the meaning it would otherwise possess. In such cases, the inventor's lexicography governs.").

2 *See, e.g., CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1231 (Fed. Cir. 2005) ("In examining the specification for proper context, however, this court will not at any time import limitations from the specification into the claims.").

3 *See, e.g., Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1374 (Fed. Cir. 2005) ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct.").

4 *See, e.g., Purdue Pharma L.P. v. Endo Pharma, Inc.*, 438 F.3d 1123, 1136 (Fed. Cir. 2006) (holding that a purported disavowal during prosecution must be clear and unambiguous to limit claim scope).

5 *See Phillips*, 415 F.3d at 1318 ("We have viewed extrinsic evidence in general as less reliable than the patent and its prosecution history in determining how to read claim terms. . . .).

ARGUMENT

A. DISPUTED TERMS FROM THE '243 PATENT

1. "Substrate"

a. The Definition of "Substrate" Set Forth In The '243 Patent Controls

Under the settled law of the Federal Circuit, the definition of "substrate" in the specification – the construction proposed by Affymetrix – controls. *See Phillips*, 415 F.3d at 1316. "Substrate" is defined in the '243 patent as "a material having a rigid or semi-rigid surface." (Affymetrix's Opening Claim Construction Brief ("Affymetrix's Br."), Ex. 7, col. 7, lines 35-36.) The next sentence following this definition, which begins "[i]n many embodiments," describes some non-limiting examples of what the surface of a substrate might be. (*Id.*, col. 7, lines 36-40.) The next sentence, which begins "[a]ccording to other embodiments," provides another possibility of what a substrate might be, such as "small beads." (*Id.*, col. 7, lines 40-43.) These sentences provide examples of "substrates," as a dictionary might provide an example of the usage of a definition, but do not alter the straightforward definition itself. As discussed below, the specification provides examples where polymers are either synthesized on a substrate or a pre-formed polymer is attached to the substrate.

Illumina, in amending its proposed construction, admits that it must account for the definition of "substrate." But Illumina then attempts to add a limitation, "on which polymers are synthesized," to that definition. This is at odds with the rule set out in *Phillips*, which provides that "the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. Illumina's attempt to circumvent the settled law of the Federal Circuit by citing misleading and incomplete portions of the specification and prosecution history also fail.

b. Illumina Ignores Portions Of The Specification That Do Not Support Its Proposed Construction

Illumina's contention that the specification only describes synthesis of polymers on a substrate is wrong.[6] The '243 specification includes a clear embodiment where a pre-synthesized polymer is attached to the substrate. Example H of the '243 patent teaches the attachment of a fully-formed peptide, Leu enkephalin, with the sequence YGGFL, to the surface of a substrate. (Affymetrix's Br., Ex. 7 ('243 patent), col. 25, line 62 through col. 26, line 27.) As discussed in this example, "[t]he Leu enkephalin sequence … *was attached* via its carboxy end to the exposed amino groups on the surface of the slide." (*Id.*, col. 26, lines 3-7 (emphasis added).) Illumina asks the Court to exclude an embodiment described in the specification in violation of a claim construction principle. *See, e.g.*, *Pfizer*, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct."). The Court should not be swayed by Illumina's selective citation to the specification and should construe "substrate" as it is defined.[7]

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[6] Illumina also states that the second sentence after the definition of "substrate" at column 7, lines 40-43, is "the only mention in the entire specification of the use of beads as a support for different polymers, as required by the asserted claims of the '243 patent." (Illumina's Opening *Markman* Brief ("Illumina's Br.") at 9.) This is incorrect. For example, the '243 specification elsewhere describes "spheres" as a substrate. (Affymetrix's Br., Ex. 7 ('243 patent), col. 10, lines 54-66.)

[7] In a further illustration of the lengths to which Illumina will go to avoid the definition provided in the specification, Illumina cites a 2002 Dictionary of Scientific and Technical Terms. (Illumina's Br. at 9 n. 2). Illumina uses the definition of the term from the electronics industry ("[ELECTR]") describing the fabrication of microcircuits rather than the definition used for biochemistry or organic chemistry – neither of which is informative here. This is exactly the kind of "dictionary shopping" that caused the *en banc Phillips* court to overrule the emphasis on dictionaries in the *Texas Digital* decision. *Phillips*, 415 F.3d at 1320-23.

c. The Prosecution History Cited By Illumina Is Irrelevant To The Construction

In an attempt to bolster its alteration of the specification's clear "substrate" definition, Illumina cites the prosecution history of the great-great-great-great-grandparent application of the '243 patent. The statements made by Affymetrix during the prosecution of the 07/492,462 application (the "'462 application")[8] do not relate to the claim terms at issue in the '243 patent. Similarly, the invention claimed in the '462 application was completely different than the invention claimed in the '243 patent. Therefore, under well-established law, the prosecution history of this grandparent application cannot be used to narrow different claim terms in different claims in a later patent. *See, e.g., ResQNet.com, Inc. v. Lansa, Inc.*, 346 F.3d 1374, 1383 (Fed. Cir. 2003) ("Although a parent patent's prosecution history may inform the claim construction of its descendant, the [predecessor] patent's prosecution history is irrelevant to the meaning of this limitation [in the patent-in-suit] because the two patents do not share the same claim language.").

The claims of the '462 application (and those of the '854 patent which issued thereon) were specifically directed to *in situ* synthesis of diverse chemical sequences. (Ex. 19 (original '462 application) at 60, claim 1.) During the prosecution of the '462 application, the Examiner rejected certain pending claims as being obvious over a Lowe prior art reference. (*See* Ex. 20 (March 20, 1991, Office Action) at 9-15.) In response, the applicants stressed that the specific invention claimed in the '462 application was distinguishable from Lowe in that it required *in situ* synthesis of an array while Lowe described only attachment of pre-synthesized materials.[9]

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8 The '462 application issued as U.S. Patent No. 5,143,854 on September 1, 1992. (Illumina's Br., Ex. S.) The '243 patent is a continuation of a continuation of a continuation of a division of a division of a division of the '462 application.

9 The Lowe reference – U.S. Patent No. 4,562,157 (Ex. 21) – is also fundamentally different than the invention claimed in the '243 patent. For example, Lowe does not

(continued . . .)

(Illumina's Br., Ex. J (August 20, 1991, Amendment) at 13-14.) The applicants also amended their claims to emphasize that this particular invention required *in situ* synthesis:

> 6. (Amended) [The method as recited in claim 1 further comprising a step of] A method of preparing and screening sequences comprising:
>
> a) exposing a first selected region of a substrate to an activator to remove a protective group;
>
> b) exposing at least said first region to a first monomer having a protective group;
>
> c) exposing a second selected region to an activator to remove a protective group, said second region at least partially overlapping said first region;
>
> d) exposing at least said second region to a second monomer so as to synthesize at least first and second sequences on said substrate; and
>
> e) screening said sequences on said substrate for affinity with a receptor, said step of screening [further] comprising [the] steps of exposing said substrate to said receptor and testing for the presence of said receptor in said first and said second region.

(*Id.* at 2.)[10] Thus, the claims of the '462 application were directed to methods of preparing and screening sequences using an array constructed through *in situ* synthesis. The applicants did not say that a "substrate" was limited to a material having a surface on which polymers are synthesized. Indeed, though the word "substrate" appears in this discussion, it is not at all the focus of either the Examiner or the applicants. *See Phillips*, 415 F.3d at 1317 (finding that the prosecution history "often lacks the clarity of the specification and thus is less useful for claim construction purposes").

(. . . continued)
disclose "an apparatus for analyzing nucleic acid binding" or a substrate comprising at least 1000 beads having nucleic acids attached.

[10] It is standard patent prosecution practice in amending claims to indicate deleted text by brackets and added text by underlining.

The claims of the '243 patent, by contrast, are *not* directed to an array constructed through *in situ* synthesis. Rather, the '243 patent claims apparatuses and methods for scanning arrays of beads, however they are made. Asserted claim 14, for example, reads as follows:

> An apparatus for analyzing nucleic acid biding, comprising:
>
> a substrate that comprises at least 1000 different spheres, beads, or particles having different species of nucleic acids attached thereto, the area of the substrate containing the at least 1000 spheres, beads, or particles being less than 1 cm^2, at least some of the nucleic acids being bound to fluorescently labeled target nucleic acids;
>
> a laser energy source to illuminate the fluorescent labels;
>
> a detector to detect a fluorescent label bound to said target nucleic acids; and
>
> a data collection system for storing fluoresced light intensity.

(Affymetrix's Br., Ex. 7 ('243 patent), col. 30, lines 53-67.) These claims, unlike those of the '462 application, say nothing about whether the nucleic acids are synthesized on or attached to the support. Statements made by Affymetrix regarding a claimed invention that was specifically directed to *in situ* synthesis cannot be used to limit a later claimed invention that is not. *See ResQNet.com*, 346 F.3d at 1383 (refusing to find the prosecution history of a related patent relevant to claim construction of the patent-in-suit "because the two patents do not share the same claim language").

In short, Illumina has improperly used statements made by Affymetrix regarding an invention that expressly required *in situ* synthesis to limit an invention that does not require *in situ* synthesis. Illumina pretends that Affymetrix made statements about what a "substrate" could be. Affymetrix did not. The applicants never suggested during the prosecution of the '462 application that a "substrate" was limited to a material having a surface on which polymers are

synthesized. Therefore, the prosecution history of the '462 application does not support Illumina's alteration of the "substrate" definition provided in the '243 patent.

2. "Target Nucleic Acids"

As discussed in Affymetrix's opening brief, "target nucleic acids" is a synonym of the term "receptor" in the '243 patent. (Affymetrix's Br. at 20-22.) The '243 patent defines "receptor" as "[a] molecule that has an affinity for a given ligand." (Affymetrix's Br., Ex. 7 ('243 patent), col. 6, lines 28-29.) Accordingly, Affymetrix proposed a construction of "target nucleic acid" – "nucleic acids that have an affinity for the nucleic acid attached to the bead" – that adopts the definition of "receptor" and matches it to the context of the claims wherein the receptor molecules are the nucleic acids in solution and the "ligand" is the nucleic acid attached to the bead.

Illumina recognizes that "target nucleic acids" is used in the same way as "receptors" in the '243 patent. (*See* Illumina's Br. at 13-14.) Nevertheless, Illumina proposes a construction that ignores the definition of "receptor" in the specification by inserting the phrase "with sequence to be determined." As the '243 patent makes clear, "receptors" can be "naturally-occurring or man-made molecules," so there is no requirement that the "target nucleic acid" has to be "the sequence to be determined" as argued by Illumina. (Affymetrix's Br., Ex. 7 ('243 patent), col. 6, lines 29-30.)

In its attempt to escape from the specification's explicit definition, Illumina tellingly turns first to extrinsic evidence – dictionary definitions and snippets of inventor testimony – to try to limit the scope of the definition provided in the specification. (Illumina Br. At 12-13). Use of such extrinsic evidence, particularly in light of the definition provided in the specification, "poses the risk that it will be used to change the meaning of claims in derogation of the indisputable public record consisting of the claims, the specification, and the prosecution

history, thereby undermining the public notice function of patents." *Phillips*, 415 F.3d at 1319 (internal quotation marks omitted). Again, Illumina turns to a 2002 dictionary for a definition that is *apropos* of nothing: "Target compound" as used by an organic chemist (so indicated in the dictionary by the notation "[ORG CHEM]") is a molecule a chemist is attempting to synthesize, not a molecule that will be interacting with another molecule in a binding event. (Illumina's Br., Ex. F (McGraw-Hill Dictionary of Scientific and Technical Terms) at 2105.)

Likewise, Illumina selects snippets of testimony that do not inform the issue: Dr. Stephen Fodor testified that

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compare Affymetrix's Br., Ex. 7, col. 6, lines 29-30.). Finally, Illumina uses testimony from Dr. William Dower, *who is not even an inventor of the '243 patent.* And, again, Illumina selectively quotes testimony, which while non-controversial, is not the entire story.

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Again, such reliance on extrinsic evidence to try to import limitations into claim language invites error. *See Phillips*, 415 F.3d at 1319.

Illumina also cites an amendment during the prosecution of the great-grandparent application to support its proposed construction. The amendment, like the specification of the '243 patent, indicates that "receptors" are synonymous with "target molecules." (*See* Illumina's Br., Ex. M (May 15, 2000, Amendment) at 2.) This amendment is consistent with Affymetrix's proposed construction, which adopts the definition of the synonymous term, "receptor." Accordingly, the Court should adopt Affymetrix's proposed construction.

B. DISPUTED TERMS FROM THE '432 PATENT

1. "Said Beads Being Coded With An Encoding System"

Illumina's argument to limit the phrase "said beads being coded with an encoding system" to an encoding system "separate from the binding polymer" relies on an incomplete and inaccurate discussion of the claims, specification, and prosecution history of the '432 and related patents and violates the basic principles of claim construction.

a. The Claims Of The '432 Patent Do Not Require That The Encoding System Be Separate From The Binding Polymer

The claims of the '432 patent do not require that the encoding system be separate from the binding polymer. (*Compare* Affymetrix's Br. at 11-12 *with* Illumina's Br. at 16.) The claims specify that the beads "have binding polymers of different target specific sequence attached thereto" and that they be "coded with an encoding system." There is no language in the claim that requires either that the binding polymer be distinct from or the same as the encoding system. Moreover, contrary to Illumina's suggestion, the claims do not specify that the attachment of the binding polymer occur after the coding of the bead. The '432 patent claims a "collection of beads," not a method for making such a collection through a sequence of particular steps.[11] The claims contemplate that the beads have binding polymers attached and have been coded with an encoding system; no preference is given to which comes first or whether they are the same thing.

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[11] Illumina's argument re-writes the claims to cover a method for making a collection of beads, comprising the steps of coding the beads with an encoding system and subsequently attaching a binding polymer. There is no support in the law for transforming a claim covering a "collection of beads" into a claim covering a "method for making such a collection." *See, e.g., Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1329 (Fed. Cir. 2003) (holding that product claims where the patentability does not depend on how the product was made are not limited to any particular method of making).

The sequence of steps hypothesized by Illumina to support its construction does not exist in the claims.

b. Illumina's Proposed Construction Conflicts With The Specification

Illumina's discussion of the specification is notable for what it fails to emphasize. On page 18 of its brief, Illumina quotes the portion of the specification describing bead encoding systems. Illumina bolds and italicizes "a magnetic system, a shape encoding system, a color encoding system, or a combination of any of these." Illumina does not bold or italicize what comes next: "or any other encoding system." (Affymetrix's Br., Ex. 6 ('432 patent), col. 21, lines 63-64.) As discussed in Affymetrix's opening brief, one of the "other encoding systems" disclosed in the patent is the use of nucleic acids (or similar binding polymers). (*Id.* at col. 58, lines 11-40.) The patent specifically states that "polymers may be used … to encode information." (*Id.* at col. 58, lines 11-13.) Illumina relegates this crucial disclosure to a footnote in its brief (Illumina Br. at 18 n.9), but it cannot change the specification: the patent envisions the use of binding polymers as an encoding system. Therefore, Illumina's proposed construction, which excludes this encoding system, violates the law. *See Pfizer*, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct.").

c. The Prosecution Of The '089 Application Does Not Support Illumina's Proposed Construction

Illumina relies on a misleading discussion of the prosecution of the parent application to the '432 patent. Application No. 09/362,089 (the "'089 application") was filed on July 28, 1999, and issued as U.S. Patent No. 6,440,667 (the "'667 patent") on August 27, 2002. The application that led to the '432 patent, a continuation of the '089 application, was filed on June 2, 2000. The '089 application and the '432 patent were prosecuted simultaneously, with the '432 patent

issuing before the '667 patent. The claims filed and ultimately issued in the two applications are substantially different – the claims of the '432 patent relate to a collection of beads while the claims of the '667 patent relate to assays which may or may not involve beads. (Affymetrix Br., Ex. 6 ('432 patent); *compare* Ex. 22 ('667 patent).) These differences, overlooked by Illumina, are important when discussing the relevance of the '089 application prosecution to the meaning of different claim terms in the '432 patent. *See, e.g.*, *ResQNet.com*, 346 F.3d at 1383 ("Although a parent patent's prosecution history may inform the claim construction of its descendant, the [predecessor] patent's prosecution history is irrelevant to the meaning of this limitation [in the patent-in-suit] because the two patents do not share the same claim language.").

During the prosecution of the '089 application, Affymetrix added claim 39:

> A method of analyzing a target molecule in a sample, comprising:
>
> (a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents and an encoding system, whereby one or more of the substrates bind to the target via the reagent;
>
> (b) separating the substrates that bind the target from the substrates that do not bind the target; and
>
> (c) identifying the reagent on a separated substrate using the encoding system.

(Ex. 23 (January 6, 2000, Amendment) at 1.) This claim was directed to an assay for identifying a target molecule in a sample. The claim did not require the use of beads.

The Examiner rejected pending claim 39 for, among other reasons, indefiniteness. (Ex. 24 (August 28, 2000, Office Action) at 4.) Affymetrix responded to this rejection by removing the "encoding system" limitation and adding a new limitation: "and an individual bound substrate thereby bears a tag of an encoding system." (Ex. 25 (February 28, 2001, Amendment) at 2.) The claim now read:

> A method of analyzing a target molecule in a sample, comprising:
>
> (a) contacting the target molecule with a collection of substrates, wherein different substrates bear different reagents [and an encoding system], whereby one or more of the substrates bind to the target via the reagent, and an individual bound substrate thereby bears a tag of an encoding system;
>
> (b) separating the substrates that bind the target from the substrates that do not bind the target; and
>
> (c) identifying the reagent on a separated substrate [using the encoding system] by reading the tag on the separated substrate.

Affymetrix explained this amendment by stating that "the reagent and the tag are different entities." (*Id.* at 9.)

The Examiner then rejected amended claim 39, in part for "lacking proper antecedent basis for 'tag of an encoding system.'" (Ex. 26 (May 15, 2001, Office Action) at 4.) Following several interviews, Affymetrix amended claim 39 to remove reference to the "tag" limitation:

> A method of identifying a target molecule in a sample, comprising:
>
> (a) contacting the target molecule with a collection of substrates, wherein different substrates bear different binding reagents and [an] a binding reagent encoding system, whereby the target molecule binds to one or more of the substrates [bind to the target] via the reagent;
>
> (b) separating the substrates that bind the target molecule from the substrates that do not bind the target molecule; and
>
> (c) identifying the reagent on a separated substrate by reading the binding reagent encoding system on the separated substrate and thereby identifying said bound target molecule.

(Ex. 27 (September 25, 2001, Amendment) at 5.) Pending claim 39 issued as claim 1 of the '667 patent. (Ex. 22 ('667 patent).)

The Federal Circuit has stated that the prosecution history of a related patent (such as a parent application) can be relevant if it addresses a limitation in common with the patent-in-suit. *Advanced Cardiovascular Sys.*, 265 F.3d at 1305. The Federal Circuit has cautioned, however,

that the prosecution history of a related patent is not relevant where there are different claim terms in dispute or the patent-in-suit and the related patent do not share the same claim language. *ResQNet.com*, 346 F.3d at 1383 (refusing to find the prosecution history of a related patent relevant to claim construction of the patent-in-suit "because the two patents do not share the same claim language"); *Advanced Cardiovascular Sys.*, 265 F.3d at 1305-06 ("Notably, there are no common claim terms in dispute.").

For example, in *ResQNet.com*, the court refused to be influenced in the claim construction process by the prosecution history of a related patent because of a relatively small difference in the claims of the patent-in-suit as compared to the claims of the related patent. The claims of the former required means for identifying a screen based upon "a position[,] length and type of *each of a plurality* of fields." *ResQNet.com*, 346 F.3d at 1382 (emphasis in original). The claims of the latter required means for generating a screen identification based upon "a function of the number, location, and length of *each* field in said first image." *Id.* (emphasis in original). The court, in refusing to consider the prosecution history of the related patent, emphasized the difference between "each of a plurality" and "each." The court concluded that the prosecution history of the related patent was "irrelevant to the meaning of this limitation [*i.e.*, "each of a plurality of fields"] because the two patents do not share the same claim language." *Id.* at 1383.

As shown above, the claims of the '432 patent are substantially different than those prosecuted in the '089 application and ultimately issued in the '667 patent. The '432 patent claims a collection of encoded beads with binding polymers attached. The claims prosecuted in the '089 application were directed to methods for identifying target molecules by using a collection of substrates. Indeed, during the prosecution of the '432 patent, Affymetrix pointed

out the substantial differences between these two applications. Following a rejection on double-patenting grounds, Affymetrix argued that "[b]y the Examiner's admission, the present claims, which are drawn to a collection of beads, are different from the assay claims of Serial No. 09/362,089." (Ex. 28 (September 17, 2001 Amendment) at 9.) The Examiner agreed and ultimately dropped the double-patenting rejection. Under the *ResQNet.com* court's reasoning, the substantial differences in the claims of the '667 patent render its prosecution history irrelevant to the interpretation of terms in the '432 patent.

Similarly, the statements made by Affymetrix during the prosecution of the '089 application upon which Illumina seeks to rely relate to a limitation that is not found in, and is therefore not relevant to, the '432 patent. After adding the limitation "and an individual bound substrate thereby bears a tag of an encoding system," Affymetrix stated that "the reagent and tag are different entities." (Illumina's Br., Ex. O (February 28, 2001, Amendment) at 9.) The '432 patent does not include the limitation "a tag of an encoding system." Statements made during the prosecution of the '089 application about the "reagent" and "tag" being different entities are irrelevant to the '432 patent, which does not claim "reagents" or "tags."[12] *See Advanced Cardiovascular Sys.*, 265 F.3d at 1305-06 ("Notably, there are no common claim terms in dispute.").

Prosecution history can narrow the scope of claim terms only where the patentee has clearly and unambiguously disclaimed claim scope. *See, e.g., Omega Eng'g, Inc. v. Raytek*

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[12] The claims as ultimately issued in the '667 patent include the limitation "a binding reagent encoding system." The claims of the '432 patent, by contrast, do not include this limitation. Rather, they require that "said beads [be] coded with an encoding system." These limitations are not the same and, given the different context of the claims, could mean different things. The differences in these issued limitations is another reason why the prosecution history of the '089 application is not relevant to construction of the phrase "said beads being coded with an encoding system" in the '432 patent.

Corp., 334 F.3d 1314, 1324-25 (Fed. Cir. 2003). The Federal Circuit requires that the alleged disavowing statement be "both so clear as to show reasonable clarity and deliberateness and so unmistakable as to be unambiguous evidence of disclaimer." *Id.* at 1325 (internal citations omitted). The statements relied upon by Illumina – which discuss different claim terms in the context of different claims from a different patent application – fall far short of any clear and unambiguous disclaimer that the "encoding system" in the '432 patent must be separate from the binding polymer. Therefore, Illumina's attempt to use the prosecution history of the '089 application to support its proposed construction should be rejected.

2. "Target Specific Sequence"

In arguing that "target specific sequence" as used in the claims of the '432 patent requires specificity for "the sequence to be determined," Illumina selectively cites to the specification and ignores embodiments that are inconsistent with its proposed construction. Affymetrix, in its opening brief, pointed to several examples in the specification (Affymetrix's Br., Ex. 6 ('432 patent) where the "target specific sequence" had specificity for a sequence other than the sequence to be determined:

- At column 27, lines 37-43: "In another embodiment, a relatively short specific oligonucleotide is used which serves as a *targeting reagent for positionally directing the sequence recognition reagent*. For example, the sequence specific reagents having a separate additional sequence recognition segment (usually of a different polymer from the target sequence) can be directed to target oligonucleotides attached to the substrate." (Emphasis added.)

- At column 34, lines 5-10: "In fact, these oligonucleotides may be used to direct other molecules to specific locations by linking specific oligonucleotides to other reagents which are in batch exposed to the matrix and hybridized in a complementary fashion to only those locations where the complementary oligonucleotide has been synthesized on the matrix."

Each of these examples makes it clear that the "target specific sequence" may serve to direct a "sequence recognition reagent" to a particular location without the "target specific sequence" being specific for the sequence to be determined. In other words, the "target specific sequence" can be specific for a manmade tag sequence that is not the sequence to be determined. The target specific sequence serves to position a "sequence recognition reagent," which in turn is specific for a sequence to be determined, at a particular location.

Illumina's proposed construction would exclude these embodiments where a reagent not specific for the sequence to be determined serves to position a sequence recognition reagent. "A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct." *SanDisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005). The *SanDisk* court explained that "[t]he court must always read the claims in view of the full specification." *Id.* The Court should reject Illumina's invitation to commit legal error and construe "target specific sequence" consistent with Affymetrix's proposal.

C. DISPUTED TERMS FROM THE '531 PATENT

1. "Probe Array"

Affymetrix and Illumina agree that the construction of "probe array" must be guided by the definitions of "probe" and "array" in the specification. (Affymetrix's Br. at 23-24; *compare* Illumina's Br. at 21.) However, Illumina adds the additional limitation that the probes be "chemically linked to a single surface." Neither the claim language, nor the specification, nor the prosecution history supports this limitation.

a. The Definitions Of "Probe" And "Array" Control

The term "probe array" combines the defined terms, "probe" and "array." Affymetrix's proposed construction combines these two definitions, while taking out the "arranged in a

spacially defined and physically addressable manner" portion of the "array" definition as it appears elsewhere in the claims and would be redundant. Where the patentee chooses to act as his or her own lexicographer, that definition controls. *Phillips*, 415 F.3d at 1316. Illumina provides no basis for importing a limitation – chemically linked to a single surface – into the definition provided by the patentees.

b. Illumina Ignores The Discussion Of Multiple Surfaces On A Support In The Specification

The '531 patent discusses the substrate and surfaces of a probe array in broad terms. (*See* Affymetrix's Br. at 24.) In particular, the statement that "*[s]urfaces* on the solid substrate usually, though not always, are composed of the same material as the substrate" demonstrates that the inventors did not intend to be limited to a single surface. (*Id.*, Ex. 8 ('531 patent), col. 9, lines 44-45 (emphasis added).) The specification goes on to state that "the surface may be composed of any of a wide variety of materials, for example, polymers, plastics, resins, polysaccharides, silica or silica-based materials, carbon, metals, inorganic glasses, membranes, or any of the above-listed substrate materials." (*Id.*, col. 9, lines 45-50.) Therefore, examples from the specification where the "probe array" is chemically linked to a single surface are not limiting.[13] *See CollegeNet, Inc.*, 418 F.3d at 1231.

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[13] Illumina also cites in passing to testimony of Dr. Richard Rava, one of the inventors of the '531 patent. (Illumina Br. at 23.)

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Even if the disclosure were completely limited to these two examples, this would not be a proper basis for importing a claim limitation. *Phillips*, 415 F.3d at 1323 ("For instance, although the specification often describes very specific embodiments of the invention, we have repeatedly warned against confining the claims to those embodiments."). And, as discussed above, the patent also discloses the use of multiple surfaces at other points in the specification that Illumina chose not to ask Dr. Rava about.

Moreover, the specification of the '531 patent incorporates by reference U.S. Patent No. 5,143,854 (the "'854 patent"), among other patents and applications, for all purposes. (Affymetrix's Br., Ex. 8 ('531 patent), col. 9, lines 11-16.) The '854 patent, which has the same specification as the asserted '243 patent, describes several embodiments where the "probe array" exists on multiple surfaces. For example, "small beads" may be used as a substrate. (Illumina's Br., Ex. S ('854 patent), col. 7, lines 55-57.) The '854 patent also provides many other examples of substrates that would have multiple surfaces, including "particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides," or any combination of these. (*Id.*, col. 11, lines 11-21.) The incorporation of the '854 patent by reference also demonstrates that the inventors did not intend to be limited to "a single surface."

c. The Prosecution History Does Not Limit The Definition Of "Probe Array"

The applicants' arguments during prosecution did not provide a clear and unambiguous disavowal of claim scope to justify altering the specification's clear definition of "probe array." *See Purdue Pharma*, 438 F.3d at 1136 (holding that a clear and unambiguous disavowal during prosecution is required to limit claim scope). In response to prior art rejections based on Affymetrix's'854 patent, amendments suggested by the Examiner were accepted by the applicants. (Illumina's Br., Ex. U (March 6, 1996, Office Action) at 3-4; Ex. Y (Notice of Allowability) at 2.) However, the prosecution history provides no reason why the amendment overcame the rejections based on the '854 patent.

Furthermore, the amendment did not materially alter the claim with respect to language regarding the "surface." Original claim 65 as filed contained the following clause:

> (b) providing a plurality of biological arrays comprising a substrate *having a surface to which is attached the plurality of arrays*;

(Illumina's Br., Ex. X ('531 Application), at 30, claim 65 (emphasis added).) The Examiner amended the clause to read:

> (b) providing a wafer *comprising on its surface a plurality of probe arrays,* each probe array comprising a collection of probes, at least two of which are different, arranged in a spacially defined and physically manner;

(Illumina's Br., Ex. Y (Notice of Allowance for '531 patent), at 2 (emphasis added).) Contrary to Illumina's arguments, the amendment, "comprising on its surface …," was not added to overcome prior art because an equivalent phrase, "having a surface to which is attached the plurality of arrays," was in the original claim. Thus, Illumina misconstrues the reason for and the significance of the amendment.

There is no statement in the prosecution history that limits the claim language to having a probe array on a single surface. *See Purdue Pharma,* 438 F.3d at 1136 ("It important to note that the claims contain no limitations relating to the effectiveness of dosages in controlling pain in patients, and it is the claims ultimately that define the invention."). The prosecution provides no evidence of a clear disavowal of the scope of "probe array," particularly in light of embodiments having multiple surfaces described in the specification. Thus, the Court should construe "probe array" consistent with the definitions in the specification as proposed by Affymetrix.

2. "Arranged In A Spacially Defined And Physically Addressable Manner"

The phrase, "arranged in a spacially defined and physically addressable manner," has no special, technical language and should be construed consistent with its ordinary meaning. Illumina bases its argument on an interpretation of a dictionary definition of "arrange" in an attempt to import a limitation of placement in a "pre-determined location." (Illumina's Br., Ex. Z (Webster's Third New International Dictionary) at 120.) Illumina's argument demonstrates why the *Phillips* court cautioned against using dictionaries without appreciating the context

provided by the specification. *See Phillips*, 415 F.3d at 1321 (noting that "dictionaries, by their nature, provide an expansive array of definitions"). As shown below, the definition of "arranged" applies equally to Affymetrix's proposed construction.

The dictionary definition of "arrange" provided by Illumina, "to put in correct, convenient, or desired order; adjust properly; dispose, place," is consistent with Affymetrix's proposed construction ("located in a particular location and capable of being accessed"). The definition says nothing about placing "in a pre-determined location" as Illumina argues. Objects may be *arranged* (*i.e.*, placed or located) without having a pre-determined location for each particular object, for example:

- The children were *arranged* in a circle for story time.
- The bowling pins were *arranged* in a triangle.
- The soldiers were *arranged* in formation.

In each of these examples, the individual members of the group (*e.g.*, children) are "located" in a particular geometric pattern without requiring that a particular child is placed in a particular location.

Likewise, all that is required of the "probes" in the claims of the '531 patent is that the "probes are arrayed on a chip in addressable rows and columns." (Affymetrix's Br., Ex. 8 ('531 patent), col. 10, lines 32-33.) This arrangement allows meaningful information to be extracted when a target sample is directed to the probe and a subsequent detection is made at that location. Illumina points to nothing in the specification or prosecution history that demonstrates an intent to limit "arranged in a spacially defined and physically addressable manner" to something narrower than its ordinary meaning. The Court should adopt Affymetrix's proposed construction because it does not import limitations from the specification.

D. DISPUTED TERMS FROM THE '365 PATENT

1. "Biological Polymers Immobilized On A Surface"

Illumina proposes a construction of "biological polymers immobilized on a surface" that would import limitations not found in the claim language and ignores examples from the patent describing multiple surfaces. While the claim language cited by Illumina reads "a surface," the Federal Circuit "has repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000); *see also CollegeNet,* 418 F.3d at 1232. "Unless the claim is specific as to the number of elements, the article 'a' receives a singular interpretation only in rare circumstances when the patentee evinces a clear intent to so limit the article." *KCJ*, 223 F.3d at 1356 (citing *Abtox, Inc. v. Exitron Corp.,* 122 F.3d 1019, 1023 (Fed.Cir.1997)). Each of the claims of the '365 patent contains the open-ended transitional phrase, "comprising." There is no language in the claims themselves or the specification to suggest that the invention is limited to a single surface. Therefore, the Court should not limit this term to a single surface. (*See* Affymetrix's Br., Ex. 9 ('365 patent), cols 23-26, independent claims 1, 2, 7, 10, 41, and 47).

As demonstrated in Affymetrix's opening brief, the specification discusses probe arrays with *multiple* surfaces. (*Id.*, col. 5, line 62 through col. 6, line 2.) The patent also describes embodiments of a probe array on a single surface.[14] The Federal Circuit has stated, however,

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[14] The '365 patent also incorporates the '854 patent by reference. (Affymetrix's Br., Ex. 9 ('365 patent), col. 1:21-26.) As discussed above in the section relating to the "probe array" term from the '531 patent, the '854 patent discusses several embodiments where the substrate is not a single surface (*e.g.*, "small beads). (*See* Illumina's Br., Ex. S ('854 patent), col. 7, lines 55-57, col. 11, lines 11-21.)

that a disclosure of a preferred or exemplary embodiment encompassing a singular element standing alone does not disclaim a plural embodiment. *KCJ*, 223 F.3d at 1356.

The *KCJ* court distinguished the situation addressed in *Insituform Tech., Inc. v. Cat Contracting, Inc.*, 99 F.3d 1098, 1105-06 (Fed. Cir. 1996), cited by Illumina. According to the *KCJ* court, the claim language at issue in *Insituform* "belied a singular meaning" because "the claim is specific as to the number of elements (one cup) and adding elements eliminates an inherent feature (discontinuous vacuum) of the claim." *KCJ*, 223 F.3d at 1356-57. Here, unlike in *Insituform*, use of multiple surfaces does not eliminate any inherent claim element. As with the situation in *KCJ*, in light of the language of the '365 claims and the associated description in the specification, there is no reason to depart from the general rule that "a" means "one or more." The Court should avoid the error inherent in Illumina's argument and adopt Affymetrix's proposed construction.

2. "Housing"

a. The Specification Does Not Require That A "Housing" Separate The Probe Array From The Atmosphere

As discussed in Affymetrix's opening brief, "housing" should be construed consistently with its widely-accepted meaning: "a structure in which something is contained." Illumina, in contrast, points to examples in the specification in an attempt to import a limitation that a housing "separates the probe array from the atmosphere." For example, Illumina argues that figures 4 and 5 of the '365 patent support its construction. The specification, however, indicates that these figures only show particular embodiments, not the entire invention. (*See* Affymetrix's Br., Ex. 9 ('365 patent), col. 7, line 65 ("FIG. 4 illustrates one embodiment of the package"); col. 8, lines 36-37 ("FIG. 5c illustrates an alternative embodiment in which cavity 310 is oriented such that the edges of the cavity 310 and the casing 410 are non-parallel.").) Nor do these

examples even address whether the described housings would in fact separate the probe array from the atmosphere.

But even if one assumes that these embodiments somehow separate the probe array from the atmosphere, the Federal Circuit has repeatedly cautioned that it is improper to import claim limitations based on embodiments in the specification. *See, e.g., CollegeNet,* 418 F.3d at 1231. Neither the language of the claims nor any portion of the specification indicates that the definition of "housing" should be limited as Illumina suggests.

b. Affymetrix's Arguments During Prosecution Did Not Even Discuss Separation From The Atmosphere

During prosecution of the '365 patent, the Examiner rejected claims for obviousness based in part on the Mitsuhashi patent. (*See* Ex. 30 (October 12, 2001), Office Action at 5-6.) Mitsuhashi described a microtiter plate with a plurality of wells, each well having a different single polynucleotide probe for hybridization. (Illumina's Br., Ex. CC (December 20, 2001, Amendment) at 14.) The applicants distinguished Mitsuhashi because it did not teach a "probe array" as claimed in the '365 patent. (*Id.*) Because Mitsuhashi does not disclose a "probe array," then, *a fortiori*, it does not disclose "a housing including a fluid cavity constructed and arranged for hybridization of a target to a probe of *said probe array*." (Affymetrix's Br., Ex. 9 ('365 patent), col. 23, lines 16-18 (emphasis added); *compare* Illumina's Br., Ex. CC at 14.) Thus, the prosecution statement cited by Illumina does not indicate a clear disavowal of claim scope. *See, e.g., Purdue Pharma*, 438 F.3d at 1136 (holding that a clear and unambiguous disavowal during prosecution is required to limit claim scope).

Moreover, the prosecution history statements regarding Mitsuhashi do not support Illumina's proposed construction that the housing has to separate a probe array from the atmosphere. Nothing in the applicants' discussion regarding Mitsuhashi relates to separation of

the probe array from the atmosphere. (Illumina's Br., Ex. CC (December 20, 2001, Amendment) at 14.) Again, Illumina attempts to take prosecution statements out of context to support its construction.

c. Illumina Selectively Cites Inventor Testimony To Support Its Proposed Construction

Illumina argues that inventor Jim Winkler's testimony "confirms" its proposed construction of "housing." Of course, inventor testimony, like other extrinsic evidence, is less reliable than the intrinsic evidence in determining how to construe claims. *See Phillips*, 415 F.3d at 1318. This is especially true if the inventor testimony is taken out of context.

Before the portion of his transcript cited by Illumina, Mr. Winkler

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This testimony is inconsistent with the requirement that the "housing" separate the probe array from the atmosphere.

Donald Besemer, another inventor of the '365 patent,

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Because Illumina has not pointed to any evidence that indicates a clear intention for "housing" to have a more limited meaning than its ordinary and customary meaning, the Court should construe "housing" to mean "a structure in which something is contained."

E. DISPUTED TERMS FROM THE '716 PATENT

1. "Probe"

a. The Specification Of The '716 Patent Does Not Limit "Probe" To A Sequence Complementary To The Sample Nucleic Acid

As stated in Affymetrix's opening brief, the parties' proposed constructions of "probe" are very similar. The difference in the constructions is that Illumina requires that the "complementary sequence" be "of the unknown sample nucleic acid." Illumina points to examples from the specification where the probe is complementary to a sequence in the sample. But nothing in the specification limits "probes" to just those examples. This is yet another example of Illumina attempting to import limitations from the specification not present in the claims. *See CollegeNet,* 418 F.3d at 1231 (Fed. Cir. 2005) ("In examining the specification for proper context, however, this court will not at any time import limitations from the specification into the claims.").

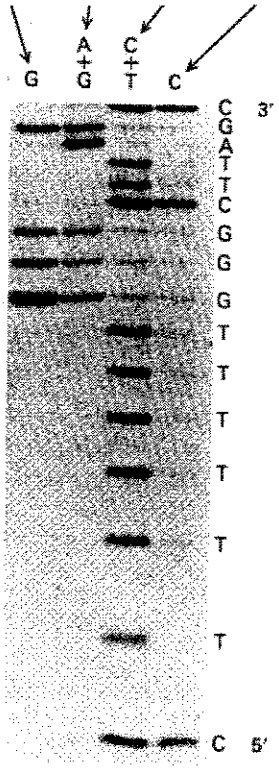
b. Illumina's Selective Citations To The Prosecution History Are Inapposite

Illumina also cites to a portion of the prosecution history in which the applicants distinguish the Weiss and Stockham patents. (Ex. 33 (Weiss); Ex. 34 (Stockham).) Weiss and Stockham relate to DNA sequencing techniques where a nucleic acid ladder (a pattern of nucleic acids that differ in length) is formed:

> Weiss and Stockham are related to nucleic acid sequencing which utilizes nucleic acid ladders which may be formed by well known techniques such as the Sanger dideoxy method or the Maxam and Gilbert method. More specifically, Weiss describes utilizing an enzyme on identical probes that hybridize with tags in the fragments of the nucleic acid ladder. The enzymes convert a

> fluorogenic substrate (*e.g.*, BBTP) into a fluorescent product in order to enhance the pattern of hybridization (see, e.g., Fig. 1C).[15]
>
> Stockham, more specifically, describes methods of sharpening signal peaks from electrophoretic migration patterns of nucleic acid ladders. Each fragment of the nucleic acid ladder is labeled with a radioactive label which is utilized to identify the position of the fragment on the gel following electrophoresis. As analyzing the migration patterns is time consuming and often error prone, Stockham describes equations and formulas for increasing the accuracy of this process (*e.g.*, sharpening signal peaks).

(Illumina's Br., Ex. DD (May 20, 1996 Amendment) at 13.) The following picture represents an "electrophoretic migration pattern[] of a nucleic acid ladder[]," as discussed by applicants:



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15 Contrary to Illumina's suggestion, these enzymes serve to generate a fluorescent signal by acting on a chemical in the solution, not by adding nucleotides to either the probe or target.

(Ex. 35 (Lodish *et al.*, *Molecular Cell Biology* (1995)) at 246.)[16] As stated by the applicants, "Weiss and Stockham are directed to identifying the location of a fragment of a nucleic acid ladder." (Illumina's Br., Ex. DD (May 20, 1996, Amendment) at 14 (emphasis in original).)

As explained in Affymetrix's amendment cited by Illumina, "Weiss uses a single probe, which will hybridize to a tag on the nucleic acid ladder fragments" and "Stockham does not utilize probes at all." (*Id.* at 13-14.) Affymetrix distinguished these references because neither describes "a *plurality* of nucleic acid probes." (Affymetrix's Br., Ex. 10 ('716 patent), col. 41, line 64 through col. 42, line 60 (emphasis added).) Moreover, to the extent Weiss uses a single probe, "each nucleic acid probe differing from each other by at least a single base." (*Id.*) Affymetrix did not distinguish Weiss and Stockham on the basis that they taught the use of "tag" probes.

In fact, Weiss teaches the incorporation of the *same* tag sequence into each of the nucleic acids in the ladder. (*See* Ex. 33 (Weiss), col. 1, lines 25-48.)[17] Weiss uses the probe as a device

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[16] As discussed in Ex. 35, page 246, this figure shows an "autoradiograph" (a method where a piece of film is exposed to a radioactively-labeled experiment) of a Maxam-Gilbert sequencing experiment (as discussed in the May 20, 1996, Amendment). This method uses different chemicals to selectively cut the DNA at different locations (at G, G+A, C+T, or C). An electric field is applied to the resulting fragments in a gel (*i.e.*, electrophoresis), which serves to separate the fragments by size. Thus, the smaller fragments will be further down in the picture because they travel faster in the gel. The sequence can then be read off the gel as a "ladder," one base at a time (*e.g.*, starting from the bottom, C-T-T-T-T …).

The Sanger method, also discussed in the May 20, 1996, Amendment, makes copies of the DNA sequence of interest using chemicals that will selectively terminate the copied strand ("dideoxy" nucleotides). The reactions generate fragments that selectively terminate at a particular base. These fragments are electrophoresed and analyzed similar to the Maxam-Gilbert sequencing method. (*See* Ex. 35 (Lodish *et al.*, *Molecular Cell Biology* (1995)) at 247.) Neither of these methods uses a "plurality of probes."

[17] Weiss also teaches the possibility of incorporating more than one tag into each fragment and successively hybridizing with different probes to achieve better resolution. (*See* Ex.

(continued . . .)

to label the fragments of the DNA ladder instead of using radioactivity as described in the *Molecular Cell Biology* textbook so that one can determine the positions of the fragments in the nucleic acid ladder (and hence the position of the tag as well). The single probe does not distinguish the identity of the different nucleic acids, nor does it "indicate an extent of hybridization." (Illumina's Br., Ex. DD (May 20, 1996, Amendment) at 13-14.) Thus, Illumina's reliance on the prosecution history to support its proposed construction is misplaced. *See Purdue Pharma*, 438 F.3d at 1136 (holding that a clear disavowal during prosecution is required to limit claim scope).

2. "Probe Intensity"

Affymetrix's proposed construction of "probe intensity" as a "detectable signal, *e.g.*, fluorescence, is consistent with the ordinary usage of the term "probe intensity" in the claims of the '716 patent. The specification uses "probe intensity" and the synonymous term, "fluorescence intensity," several times to refer to the detectable signal relating to a probe. (*See, e.g.*, Affymetrix's Br., Ex. 10 ('716 patent), col. 11, lines 38-39; col. 22, lines 11-12; col. 23, line 23; col. 24, line 7; col. 25, line 27-28.) All that is required of a "probe intensity" is that it indicates an extent of hybridization.

Illumina seeks to add two limitations to this claim term: (1) that the intensity be generated by a "labeled sample" and (2) that the sample be hybridized to a "probe location." To support its construction, Illumina cites to examples from the specification where there is a labeled nucleic acid hybridized to the target and where samples are hybridized to probe

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(. . . continued)

33 (Weiss), col. 17, lines 14-28.) But in each of the hybridization steps, only one probe is used, and the different hybridizations are used to confirm the locations of the fragments of a nucleic acid ladder in the gel.

locations. These examples, however, are non-limiting. There is no mention in the specification that this is the invention itself or that there is a clear intention to limit the claim scope "using words of manifest exclusion or restriction." *Gemstar-TV Guide Int'l, Inc. v. International Trade Comm'n*, 383 F.3d 1352, 1366 (Fed. Cir. 2004) (vacating construction that improperly imported limitations without a clear disavowal of scope). As discussed in Affymetrix's opening brief, there are many ways to generate a detectable label that indicates an extent of hybridization. One could label the sequence that hybridizes to the probe before hybridization or label the probe or the hybrid after hybridization. Likewise, the probe may be in solution at the time of hybridization and later be detected at a location.

Illumina also adds a limitation that there must be a "probe location" in its proposed construction. As discussed in Affymetrix's opening brief, Illumina's proposal violates the principle of claim differentiation. The *en banc* Federal Circuit in *Phillips* explained that "the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips*, 415 F.3d at 1315. Here, dependent claim 9 adds the limitation that the "nucleic acid probes are in an array of probes." (Affymetrix's Br., Ex. 10 ('716 patent), col. 46, lines 5-6.) An "array of probes" requires that the probes have a location. The presence of this additional "probe location" limitation in claim 9 (*i.e.*, "an array of probes") demonstrates that the independent claims do not require a "probe location."

Illumina also misconstrues to the applicants' arguments distinguishing the Weiss and Stockham patents to bolster its proposed construction. As discussed above, Weiss and Stockham relate to a very different technology – nucleic acid sequencing by electrophoresis migration patterns of nucleic acid ladders. There is no "plurality of probes" to provide "probe intensities"

indicating an extent of hybridization. To the extent a single base is used to visualize the fragments, it does not differ by at least a single base. Because Weiss and Stockham do not provide a plurality of probes, these references cannot have described "probe intensities" as required by the '716 claims. In drawing out these distinctions, Affymetrix did not clearly disavow the claim scope of "probe intensity" in distinguishing Weiss and Stockham. Accordingly, the Court should construe "probe intensity" consistent with Affymetrix's proposal.

3. "Corresponding To Probe Intensities For A Plurality Of Nucleic Acid Probes"

Affymetrix proposes a construction of this term that takes into account the disclosure in the specification. Illumina's proposed construction on the other hand imports a limitation ("each having one and only one probe intensity") that directly contradicts an embodiment in the specification. The "Pooling Processing" section of the specification describes an experiment where a reference nucleic acid and a sample nucleic acid, each labeled with a different fluorescent (or other) marker, are processed together on an array:

> The present invention provides pooling processing which is a method of processing reference and sample nucleic acid sequences together to reduce variations across individual experiments. In the representative embodiment discussed herein, the reference and sample nucleic acid sequences are labeled with different fluorescent markers emitting light at different wavelengths. However, the nucleic acids may be labeled with other types of markers including distinguishable radioactive markers.
>
> After the reference and sample nucleic acid sequences are labeled with different color fluorescent markers, the labeled reference and sample nucleic acid sequences are then combined and processed together. An apparatus for detecting targets labeled with different markers is provided in U.S. application Ser. No. 08/195,889 and is hereby incorporated by reference for all purposes.

(Affymetrix's Br., Ex. 10 ('716 patent), col. 21, lines 35-51 (emphasis added).)

Figure 7 of the '716 patent also shows the combining of the differently-labeled reference and sample sequences for analysis:

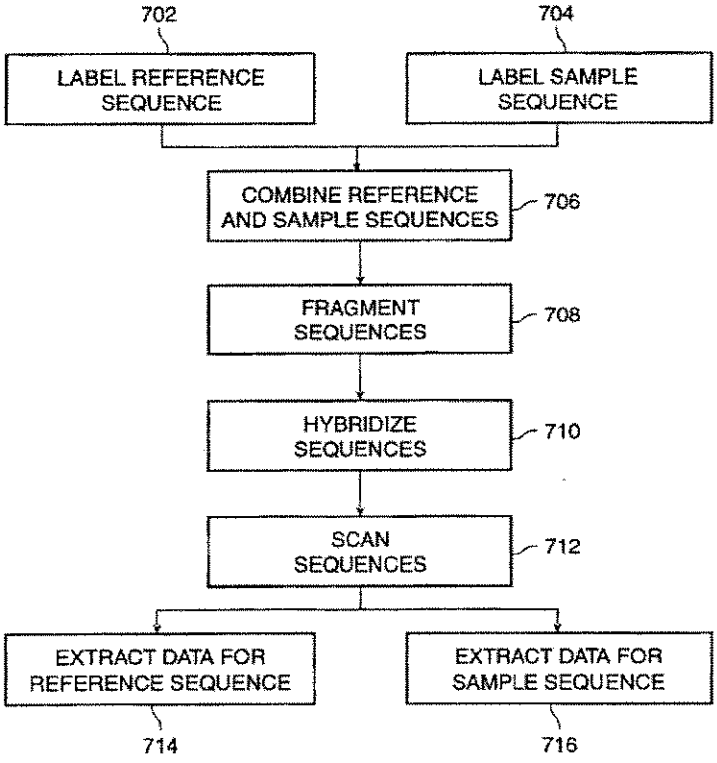

FIG. 7

(*Id.*, Fig. 7.) These disclosures demonstrate that the inventors intended to cover situations where more than one probe intensity (from the different labels) comes from one location (an area with multiple copies of the same probe).

This point is reinforced by the incorporation by reference of application serial no. 08/195,889, which issued as U.S. Patent No. 5,631,734 (the "'734 patent"), in the discussion of "Pooling Processing." (Ex. 36 ('734 patent) front page.) The '734 patent describes a fluorescence detection device that detects two fluorescent dyes: "However, the embodiment in FIG. 1c provides means for detecting a second fluorescent color. Two-color detection is required when two different types of targets, each labeled with a different dye, are exposed to a substrate

synthesized with probes." (*Id.*, col. 8, lines 33-37.) The incorporation of the '734 patent demonstrates that the applicants meant that the "Pooling Processing" method could lead to multiple probe intensities at a single location.[18] Indeed, labeling and detecting an experiment combining two samples with two different colors would be nonsensical if each and every probe location could only have one intensity.

Illumina cites to a portion of the '716 patent prosecution relating to a discussion of "how a single probe can have more than one intensity." (Illumina's Br., Ex. FF (December 19, 1995, Office Action) at 3.) Illumina misconstrues this statement in an attempt to support its construction. The Examiner's question quoted by Illumina refers to whether a single probe molecule can have more than one intensity. It cannot.

A single probe location or "feature," however, can have more than a single probe intensity because there are many probe molecules with the same sequence at that location. In fact, each location may have many thousands of copies of the same probe molecule. The "Pooling Processing" procedure teaches that an area with many copies of the same probe can have two intensities where differently-labeled reference and sample sequences bind to different copies of the same probe within that feature. In other words, in a single probe location, about half the probe molecules could bind to a sample having one intensity (*e.g.*, a green label) and half the probes have another intensity (*e.g.*, a red label). Therefore, Illumina's proposed construction is not supported by the prosecution history and would exclude a disclosed embodiment. *See*

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[18] The '734 patent also has a definition of "probe" – "a molecule that is recognized by a particular target" – that is consistent with Affymetrix's proposed construction. (*Id.*, col. 3, lines 14-15.) In the discussion of the definition of "target," it is noted that a "target" may be "naturally-occurring or manmade molecules." (*Id.*, col. 3, lines 24-25.)

Pfizer, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct.").

4. "Indicating An Extent Of Hybridization"

Affymetrix's proposed construction takes into account the plain meaning of this phrase. Illumina's construction, in contrast, seeks to add a purpose to the phrase ("so as to distinguish a single-base mismatch") that is not found in the claim language. The claim language already provides a purpose for why the claimed computer programs or systems use probe intensities "indicating an extent of hybridization" – it is to "generate a base call." (*See, e.g.*, Affymetrix's Br., Ex. 10 ('716 patent), claim 1.) As Affymetrix will demonstrate from the specification, these purposes, while seemingly similar, lead to different results in the software.

The specification provides several examples where the computer program does not distinguish a single base mismatch. In column 9, at lines 14-35, the specification describes a situation using the ratio method where the ratio of the normalized intensities of the two highest intensity probes is 1.05. (*Id.*, col. 9, lines 22-23.) Because this ratio is below the cutoff of 1.2, the program cannot distinguish which probe ("C" or "A") has a single-base mismatch. (*Id.*, col. 9, lines 23-25). Even though the single-base mismatch cannot be distinguished, the computer program generates a base call "K" that indicates the ambiguity. (*Id.*, col. 9, lines 31-35.) The "K" call indicates a likelihood that either "A" or "C" is present at that position. Illumina's proposed construction would exclude improperly several exemplary algorithms where a single-base mismatch cannot be distinguished. *See Pfizer*, 429 F.3d at 1374.

Illumina also cites prosecution history relating to the Weiss and Stockham patents. As discussed above, Stockham does not disclose *any* probes. Without any probes, Stockham does not entail hybridization at all. Weiss, on the other hand, uses a single probe, rather than a "plurality of nucleic acid probes … differing from each other by at least a single base" as

claimed in the '716 patent. The cited prosecution pointed out this fundamental difference between the '716 patent claims and the Weiss and Stockham patents. Neither Weiss nor Stockham use "an extent of hybridization" in analyzing the nucleic acid ladder because Weiss uses a single probe that is present in all the nucleic acid fragments in the ladder, while Stockham does not use a probe at all. The Court should construe "indicating an extent of hybridization" to mean "relating to the relative binding of."

5. "Comparison Of Said Plurality Of Probe Intensities To Each Other"

Affymetrix's proposed construction of this term encompasses the many different types of "comparisons" that are described in the specification. Among the various types of comparisons, the specification of the '716 patent teaches ranking of probe intensities, calculating ratios between probe intensities, and statistical methods based on the variance from experiment to experiment. (*See, e.g.,* Affymetrix's Br., Ex. 10 ('716 patent), col. 9, lines 2-13.) The plain meaning proposed by Affymetrix is consistent with the range of "comparisons" described in the specification.

Illumina seeks to limit the construction to one particular type of "comparison": a ranking. To support its proposed construction, Illumina ignores embodiments that do not require a ranking, for example, calculating a ratio. Contrary to Federal Circuit holdings, Illumina's proposed construction would exclude these embodiment. *See Pfizer,* 429 F.3d at 1374.

Illumina further cites to the prosecution history where the applicants responded to the Examiner's indefiniteness rejection by pointing to examples of comparisons in the specification. The applicants did not list all the comparisons covered by the claims, but provided examples of comparisons for the Examiner:

> With regard to claim 60, the Examiner indicated it is not clear to what the probe intensities are compared. Applicants amended

> claim 60 to recite[] that the probe intensities are compared to each other (*see, e.g.*, Figs. 3, 4A and 5).

(Illumina's Br., Ex. HH (January 9, 1997, Amendment) at 14 (emphasis added).) The point of the amendment was that the probe intensities are compared to each other, pointing to some examples in the specification without intending to be limited by those excerpts ("*see, e.g.*"). The applicants certainly did not limit the comparison to a "ranking." Because there is no clear disavowal of different ways of performing a "comparison" in the prosecution history, the Court should adopt Affymetrix's plain meaning construction.

6. "Generates A Base Call Identifying Said Unknown Base"

As discussed in Affymetrix's opening brief, the parties generally agree on the construction of "generates a base call identifying said unknown base." The claimed computer programs and systems do not purport to identify a base categorically, but rather predict which base is most likely to be present. (*See* Affymetrix's Br., Ex. 10 ('716 patent), col. 15, lines 3-6 (discussing an improved method "resulting in more accurate base calling"); col. 21, lines 32-33 ("The statistical method has also been used to implement confidence estimates . . . ."); col. 13, lines 23-47 (assigning confidence codes to the "base call").) While an "A, C, G or T (or U)" is often the base call, there is no requirement that the call result in an absolute identification of a nucleotide as one of the four possible bases. As discussed above regarding the "indicating an extent of hybridization" term, the described algorithms sometimes gave a call (*e.g.*, "K") that serves to indicate that the base was likely to be one of two different nucleotides.

In opposing this construction, Illumina blatantly mischaracterizes the position taken by Affymetrix in the *Hyseq* litigation. In that case, the parties sought construction of "computer code that generates a base call identifying said unknown base" from claims 3 and 4.

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Illumina does not cite this proposed construction, which is not at odds with Affymetrix's proposed construction. Rather, Illumina points to a statement Affymetrix made in its brief to provide background for the '716 patent, not a construction of any claim term. This background statement is irrelevant to the construction of the term, "generates a base call identifying said unknown base." The Court should adopt Affymetrix's proposed construction.

7. "Generates A Base Call . . . According To Results Of Said Comparison And Said Sequences Of Said Nucleic Acid Probes"

As discussed in Affymetrix's opening brief, this phrase need not be separately construed. It is a collection of several phrases and terms – "generates a base call identifying said unknown base," "comparison," and "probe" – that have already been construed. Illumina's argument that Affymetrix's position ignores the requirement of a "comparison" is wrong. Affymetrix has already provided a construction of "comparison."

In proposing its construction of this phrase, Illumina repeats the erroneous argument it makes regarding the "comparison" term – namely, Illumina requires that a ranking be performed. As discussed above, there is no requirement in the claims or the specification that the base call be predicated on the highest probe intensity or a ranking of probe intensities. The patent provides many examples of "comparisons" that do not require a ranking of probe intensities.

Illumina's discussion of the prosecution history is equally unavailing. In the amendment cited by Illumina, the applicants informed the Examiner that the "specification provides full detail on possible 'comparing' and 'generating' (as amended) steps." (Illumina's Br., Ex. HH (January 9, 1997 Amendment) at 15.) The applicants then went on to provide an example of

such a comparison: "*For example*, the highest probe intensity may be compared to the next highest probe intensity to generate a ratio." (*Id.* (emphasis added).) The use of the term "for example" confirms that the applicants were describing one embodiment, not the entire invention. Illumina ignores this crucial fact in its attempt to use the prosecution history to narrow the claims. The applicants did not express an unambiguous intent to limit themselves to this example. *See, e.g., Omega Eng'g,* 334 F.3d at 1325 (requiring that an alleged disavowing statement be "both so clear as to show reasonable clarity and deliberateness and so unmistakable as to be unambiguous evidence of disclaimer").

CONCLUSION

Based on the foregoing, Affymetrix respectfully requests that the Court construe the claim terms as proposed by Affymetrix.

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